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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
YAEN, CHRISTOPHER H	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 04/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/642,660	SCHNECK ET AL.	
	Examiner	Art Unit	
	Christopher H. Yaen	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-32 and 51-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-32 and 51-58* is/are rejected.

7)☒ Claim(s) *59 and 60* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 August 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/11/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Re: SCHNECK *ET AL*

1. The amendment filed 1/11/2006 is acknowledged and entered into the record. Accordingly, claims 1-27 and 33-50 are canceled without prejudice or disclaimer.

2. Claims 28-32 and 51-60 are pending and examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

4. The Information Disclosure Statement filed 1/11/2006 is acknowledged and considered. A signed copy of the IDS is attached hereto.

Claim Rejections Maintained - 35 USC § 112, 1st paragraph

5. The rejection of claims 32, and 56-58 under 35 USC § 112, 1st paragraph as lacking adequate written description is maintained for the reasons of record. Applicant argues that the instantly claimed recitation of the term "antigenic peptide" is adequately supported in the specification as filed. Specifically, applicant argues that what is well known and available in the art need not be specifically taught or disclosed in the specification. Applicant then indicates that "antigenic peptides" are neither new nor unconventional in the art. Applicant direct the examiner to the arguments presented in the reply filed 3/8/2005. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record.

In deciding *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997), the Federal Circuit held that a generic statement that defines a genus of nucleic acids *by only their functional activity* does not provide an adequate written description of the genus. By analogy, a generic statement that defines a genus of "antigenic peptides" by only their common ability bind to the peptide binding site of an MHC or to the peptide binding site of a T-cell receptor TCR, as argued in the response filed 3/8/2005 does not serve to adequately describe the genus as whole. The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members. In this case, applicant has not specifically disclosed any particular structure or correlated any structure with any particular function, because the binding of the peptides to the MHC or TCR is not a function of the peptide per se, but rather a characteristics of the peptide. Moreover, "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Furthermore, the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568). In this instance, as in that, there is no language that adequately describes with the requisite degree of particularity necessary to satisfy the written description requirement the of the genus of structurally variable polypeptides encompassed by the claimed "antigenic peptides". Again, a description of what a material does, rather than of what it is, does not suffice to describe the claimed invention. It is also aptly noted that with regard to the binding of an antigen to the TCRs, the antigenic peptide itself is incapable of binding to the TCRs in the absence of presentation by the MHCs. Therefore, the function ascribed to the "antigenic peptide" does not adequately define the genus as so claimed.

Therefore, the rejection of claims under 35 USC § 112, 1st paragraph is maintained for the reasons of record.

Claim Rejections Maintained - 35 USC § 103

6. The rejection of claims 28-31 and 51-55 under 35 USC § 103(a) as being obvious over Matsui *et al* in view of Del Porto *et al* (Proc. Natl. Acad. Sci., USA 1994; 91(26):12862-12866), Chang *et al* (Proc. Natl. Acad. Sci., USA 1994; 91(24):11408-11412) and Harris *et al* (WO 94/09131) is maintained for the reasons of record.

Applicant argues that the Office Action does not consider the invention as a whole and has not considered the entirety of any of the references. When properly considered the cited prior art does not render any of claims 28-31 and 51-55 *prima facie* obvious. The response argues that the teachings of Matsui *et al* would not have motivated one of ordinary skill in the art to seek high affinity, soluble divalent TCR/IgG and class II MHC/IgG molecules because although Matsui acknowledges that low affinity interaction between soluble TCRs and soluble peptide/MHC, Matsui uses surface plasmon resonance to overcome the disadvantages of indirect measurements. Matsui *et al* provides no suggestion that the affinity of these molecules should be modified and none of the secondary references make up for the deficiencies of Matsui. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record.

The examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that an "express, written motivation to combine must appear in prior art references before a finding of obviousness." See Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). For example, motivation to combine prior art references may exist in the nature of the problem to be solved (Ruiz at 1276, 69 USPQ2d at 1690) or the knowledge of one of ordinary skill in the art (National Steel Car v. Canadian Pacific Railway Ltd., 357 F.3d 1319, 1338, 69 USPQ2d 1641, 1656 (Fed. Cir. 2004)). References are evaluated

by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In this case, the solution provided by Matsui does not actually solve the low affinity interaction between soluble MHC heterodimers and TCRs and would be of little practical use, such as inhibiting the lysis of target cells by alloreactive MHC-specific T cells, which require a high affinity interaction between MHC heterodimers and TCRs as taught by Dal Porto *et al*. The teachings of Dal Porto *et al* indicate that divalent class I MHC/IgG molecules have increased affinity for TCRs relative to the interaction between monovalent MHC class I and T cells (TCRs) (i.e., nanomolar verses micromolar affinity) and soluble divalent MHC(H-2Kb)/IgG molecules specifically inhibited lysis of target cells by alloreactive H-2Kb-specific T cells, whereas soluble monovalent MHC (H-2Kb) never inhibited the response of alloreactive H-2Kb-specific T cells to cells expressing native H-2Kb. Thus, there would be an advantage to producing soluble divalent TCR/IgG and class II MHC/IgG molecules to solve the low affinity problem of soluble monovalent forms of TCRs and MHC heterodimers, which has limited their use according to Matsui *et al*. Further, the teachings of Chang *et al* indicating that the generation of soluble TCR molecules is hampered by inefficient pairing of alpha and beta subunits in the absence of their respective transmembrane regions and the fusion of self-associating polypeptides to the C-termini of the TCR alpha and beta extracellular segments promotes heterodimer formation over homodimer formation, making it possible to facilitate the association of any type of naturally occurring heterodimeric structure including MHC class II alpha and beta subunits, which would have suggested to one of ordinary skill in the art to modify Dal Porto's soluble

divalent class I MHC/IgG molecular complex by fusing both TCR alpha and beta extracellular segments to the N-terminus of the heavy and light chains, respectively, to facilitate heterodimer formation. Thus, when evaluating the references as a whole based on what they suggest to one versed in the art rather than by their specific disclosures, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art.

The response continues to argue that the teachings of Chang *et al* would not have led one of ordinary skill in the art to use an immunoglobulin molecule to produce the claimed molecular complex and applicant points out the differences between leucine zippers and immunoglobulin chains and cites Abbas *et al* for support (pg. 6 of the response). The response argues the art of Dal Porto *et al* by stating that they teach a molecule that differs substantially from the recited molecular complex (pg. 7 of the response). Applicant points out that the key difference is that the instantly recited molecular complexes comprise two different fusion proteins (see Fig 1D at pg. 7 of the response) and modifying Dal Porto's molecule to arrive at the present molecular complex would have involved two modifications: (1) fusing the extracellular domain of a first polypeptide to the immunoglobulin heavy chain in place of the class I MHC alpha chain and (2) fusing the extracellular domain of a second transmembrane polypeptide to the immunoglobulin's light chain, all of which Dal Porto *et al* do not teach or suggest. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record.

As noted by Applicant, the presently claimed molecular complexes merely differ from the molecular complex of Dal Porto *et al* by substitution of the extracellular domains (alpha and beta subunits) of the TCR and class II MHC molecules in place of the class I MHC portion of the molecule of Dal Porto *et al*. Thus, the presently claimed molecular complexes are not substantially different from the molecular complex of Dal Porto *et al*. It is reiterated that one of ordinary skill in the art would have been motivated to modify Dal Porto's soluble divalent class I MHC/IgG molecular complex by fusing the C-terminus of both TCR alpha and beta extracellular segments to the N-terminus of the heavy and light chains, respectively, to facilitate heterodimer formation because Chang *et al* teaches that the generation of soluble TCR molecules is hampered by inefficient pairing of alpha and beta subunits in the absence of their respective transmembrane regions and the fusion of self-associating polypeptides to the C-termini of the TCR alpha and beta extracellular segments promotes heterodimer formation over homodimer formation, making it possible to facilitate the association of any type of naturally occurring heterodimeric structure including MHC class II alpha and beta subunits. One of ordinary skill in the art would have had a reasonable expectation of success in making the above modification because Harris *et al* evince that binding domains (including cell surface receptors) can be fused via a linker to the N-terminus of the heavy and light chain variable regions without altering the binding function of the fusion proteins. The examiner acknowledges Applicant's criticism of the Office Action regarding the teachings of Harris *et al* (pg. 6 of the response), however, Applicant is again reminded that, one cannot show nonobviousness by attacking references

individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981)*, In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant continues to argue by indicating, that those of skill in the art knew that no particular manipulation was needed to cause the extracellular domain of MHC class II molecules or TCRs to associate to form functional binding sites. Even if, *arguendo*, one of ordinary skill had been motivated to modify Dal Porto's molecule to produce those instantly claimed, the logical approach would have been to express one extracellular domain by itself and permit the two extracellular domains to associate as the prior art taught they would, however, this is not the present invention. None of the prior art motivates the ordinary skilled artisan to take the extra step of fusing the other extracellular domain to the immunoglobulln light chain. Applicant support this argument by citing the state of the art (i.e. US Patents 5,723,309 and 5,583,031) and indicates that those of skill in the art would not have thought to modify or manipulate the molecules. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record.

As discussed above, Chang *et al* indicate that the generation of soluble TCR molecules is hampered by inefficient pairing of the alpha and beta subunits and the fusion of self-associating polypeptides to the C-termini of the TCR alpha and beta extracellular segments promotes heterodimer formation over homodimer formation, making it possible to facilitate the association; of any type of naturally occurring heterodimeric structure including MHC class II alpha and beta subunits, providing

explicit motivation to modify the soluble divalent class I MHC/IgG molecule of Dal Porto *et al* by fusing both MHC class II alpha and beta extracellular segments or fusing both TCR alpha and beta extracellular segments via a peptide linker to the heavy and light chain variable regions to efficiently pair the alpha and beta extracellular segments in the absence of their respective transmembrane regions and facilitate heterodimer formation. Further, the logical approach would have been to produce class II MHC/IgG and TCR/IgG molecular complexes that are structurally similar to the class II MHC and TCR as they exist naturally, rather than produce class II MHC/IgG and TCR/IgG molecular complexes that are more similar to structurally different class I MHC/IgG molecular complex in that class I MHC molecules only have one transmembrane domain and a self- associating beta-2 microglobulin subunit, whereas both class II MHC and the TCR consist of two chains, alpha and beta, that are each anchored on the cell membrane by transmembrane segments.

Applicant finally argues that the PTO has used the present specification as a template to select isolated teachings of the cited references and to modify and combine them without regard to what each of the references teaches as a whole. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin,

443 F.2d 1392 170 USPQ 209 (CCPA 1971). Again, using only the teachings in the cited references and as discussed above one of ordinary skill in the art would have been motivated and had a reasonable expectation of success at the time the invention was made to modify the soluble divalent MHC class I/IgG molecule of Dal Porto *et al* to produce soluble divalent class II MHC/IgG and soluble divalent TCR/IgG molecular complexes by fusing both MHC class II alpha and beta extracellular segments or fusing both TCR alpha and beta extracellular segments via a peptide linker to the N-terminus of the heavy and light chain variable regions because Chang *et al* teach that the generation of soluble TCR molecules is hampered by inefficient pairing of the alpha and beta subunits and the fusion of self-associating polypeptides to the C-termini of the TCR alpha and beta extracellular segments promotes heterodimer formation over homodimer formation and Harris *et al* provides a reasonable expectation of success because Harris *et al* shows that binding domains can be fused via a linker to the N-terminus of the variable regions of immunoglobulin heavy and light chains without altering the binding function of the fusion proteins. Further, one of ordinary skill in the art at the time the invention was made would have been motivated to produce soluble divalent TCR/IgG and class II MHC/IgG molecular complexes for selectively suppressing specific T cell responses and overcome the practical limitations of low affinity soluble monovalent forms of TCRs and MHC heterodimers as taught by Matsui *et al* and Dal Porto *et al* .

Therefore' the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references and the rejection is maintained for reasons of record and reiterated herein.

Conclusion

No claim is allowed. Claims 59 and 60 are objected to as being dependent on rejected claims.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H. Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher Yaen, Examiner
Art Unit 1643
April 10, 2006

CHRISTOPHER YAEN
PATENT EXAMINER